Ear Nose Throat Pathologies

Introduction

This lesson focuses on **upper airway** pathologies and their mechanisms. "Upper airway" here includes the nasal cavity, middle ear, oropharynx, nasopharynx, and larynx. Disorders of these structures are among the most common afflictions of humans. Fortunately, the overwhelming majority of these disorders are more annoying than harmful, and those that are harmful can either be vaccinated against or are exceedingly rare. We've divided the upper airway into two groups: the respiratory epithelia of the nasal cavity, paranasal sinuses, middle ear, and trachea (which get infected), and the stratified squamous epithelia of the nasopharynx, oropharynx, and larynx (which get infected and can transform into cancer).

You will see a common theme—certain bacteria prefer certain epithelia. We've divided the lesson up anatomically, starting on the outside and working our way down the airway. If, instead of thinking about the diagnoses in terms of their anatomical location, you start thinking about the epithelia that line those parts, patterns will emerge. If the epithelium is stratified squamous, it gets infected by group A *Strep. pyogenes* and *Staph. aureus*. If the epithelium is respiratory, it gets infected by *Strep. pneumo*, *Moraxella*, and *Haemophilus*.

Nasal Cavity and Paranasal Sinuses

The conditions that affect the nasal cavity and paranasal sinuses are those that affect the respiratory epithelium, mucus secretion, and obstruction of the sinuses. We start with infectious etiologies—rhinitis, sinusitis—then transition to other noninfectious conditions of the nasal cavity and paranasal sinuses.

Viral rhinosinusitis. Rhinitis is inflammation of the mucosa of the nasal cavity itself. **Rhinorrhea** is the discharge of mucus from the nose. **Infectious rhinitis** is caused universally by a **viral infection**. The coronavirus, adenovirus, and rhinovirus we studied in Microbiology cause infectious rhinitis. These viruses have tropism for mucosal cells, specifically ciliated columnar cells. The viruses function only at cooler temperatures (36˚C), so they stay restricted to the nasal cavity rather than going deeper. Viral infection summons a $CD8^+$ cytotoxic T lymphocyte response to quell it. In the process, vasodilation and infiltration of the mucosa cause swelling, leading to a restriction of airflow (a stuffy nose). Excess mucus secretion leads to rhinorrhea (runny nose), and the mild inflammatory response to a peripheral invader causes systemic viral symptoms. **Clear rhinorrhea, mild aches** and **mild malaise**, and a **mild fever** characterize a viral nasal cavity infection. Infectious rhinitis is annoying. Most of the time, it gets better on its own and there are no sequelae. Sometimes the inflammation can predispose the patient to bacterial sinusitis.

Sinusitis. The same epithelium that lines the nasal cavity lines the paranasal sinuses. The same viruses that can get to the nasal cavity can get to the sinuses and infect the lining of the cavity. Therefore, the most common causes of **infectious sinusitis** are the same viruses that cause infectious rhinitis. The only difference between viral rhinitis and viral sinusitis is the presence of sinus pressure. Most of the time, viral sinusitis runs its course with no sequelae. However, the passages that drain the sinuses into the nasal cavity are smaller than those that drain the nasal cavity, meaning there is a much higher likelihood of the "viral inflammation" that leads to the obstruction of drainage from the sinuses. Those passages are contained within the meatus between turbinates. Whenever there is an obstruction, fluid accumulates. The accumulation of fluid in a sinus causes **pain**. Worse, obstruction of a hollow tube is the predisposing pathology surrounding bacterial superinfection. **Bacterial sinusitis** is rarer than viral sinusitis, but it is more dangerous. Bacterial sinusitis will present as **purulent drainage** from the nose, a real **fever**, and **facial tenderness**. It often follows viral sinusitis—the patient gets better initially, then precipitously worse. Adults tend to get sinusitis in the **maxillary sinus** because it drains against gravity. Bacterial sinusitis is an infection of the respiratory epithelium, so it is caused by the respiratory epithelium bacteria *Strep. pneumo*, *Moraxella*, and *Haemophilus*. Treatment is with antibiotics, usually β-lactams.

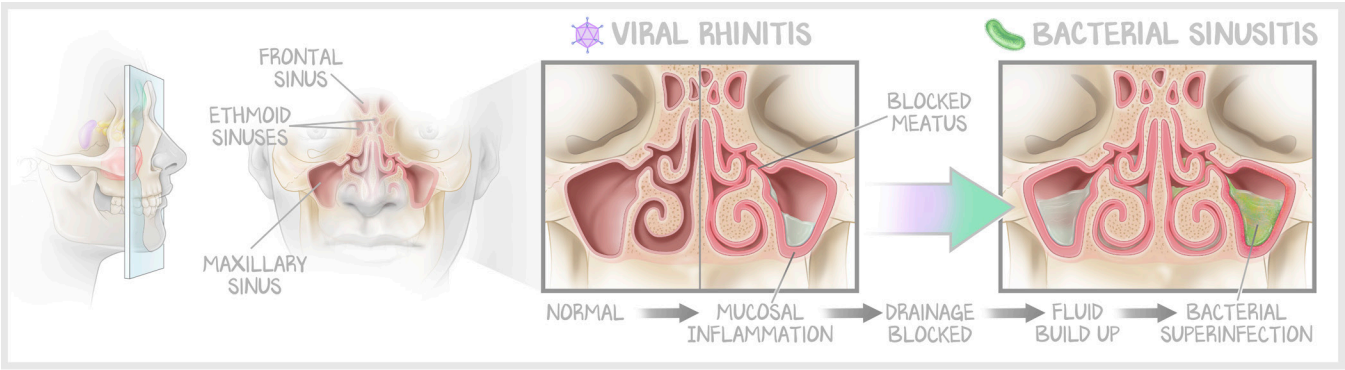

Figure 2.1: Rhinitis and Sinusitis
The initial inflammation induced by a viral infection can lead to an obstruction of the meatus that drains the sinus. The sinus accumulates mucus, which on its own can hurt. In addition, fluid stagnation predisposes the patient to bacterial superinfection. Most bacterial sinusitis follows a viral infection of the nasal or sinus epithelium.

Necrotizing sinusitis. Patients with diabetes who are in DKA and have a fungus in their nasal cavity that is boring into their brain have **mucormycosis**. That's technically a fungal sinusitis. However, mucormycosis necrotizing sinusitis will not present as maxillary pain and purulent drainage and leave you wondering whether this is fungal or bacterial. It will present as a patient with diabetes who is in DKA and has a fungus boring into their brain and out of their face. Similarly, **granulomatosis with polyangiitis** (formerly the eponym Wegner's granulomatosis) is also a vasculitic sinusitis. But it does not present as maxillary pain and purulent drainage and leave you wondering whether this is a life-threatening inflammation of the blood vessels or a bacterial infection. It will present as hemoptysis, hematuria, and anything to do with the nasal passage (Renal: Injury #3: *Introduction to Glomerulonephritis*). It's the frank blood in the urine and coughing up of blood that will catch your attention. It displays a pauci-immune immunofluorescent pattern and has crescents in the glomeruli on light microscopy. Also, no maxillary pain or purulent drainage. You won't mistake mucormycosis or Wegner's as 'sinusitis.'

Allergic rhinitis. When there is no viral infection of the epithelium, but the symptoms of infectious rhinitis are present, think allergic rhinitis. It is caused by a **type 1 hypersensitivity reaction** (IgE, mast cells, eosinophils) and is commonly seen in other atopic diseases—allergies, atopy, and asthma. And, like asthma, if biopsied, there will be the presence of eosinophils. This is not seasonal allergies that we treat with over-the-counter antihistamines, and it doesn't present in isolation. Look for a history of atopy and diagnose it in children (similar to asthma and atopic dermatitis).

Nasal polyps. Recurrent attacks of rhinitis may eventually lead to focal protrusions of the mucosa, producing so-called nasal polyps, which may reach 3–4 cm in length. On histologic examination, these polyps consist of edematous mucosa with a loose stroma, often harbor hyperplastic or cystic mucous glands, and have a variety of inflammatory infiltrates, including neutrophils, eosinophils, and plasma cells, with occasional clusters of lymphocytes. You should associate nasal polyps with a patient who has **asthma** and allergies; expect atopy. The physical exam finding will be provided to you in a vignette to ensure the diagnosis of atopy.

Choanal atresia and stenosis. The back of the nasal cavity, the space where the respiratory epithelium of the nasal cavity transitions to the epithelium of the esophagus, is the choana. The nasal cavity is derived from the gut tube. The gut tube undergoes overproliferation and recanalization, as we saw in the development of the gut tube and the development of the trachea. Just as with esophageal or tracheal atresia, if recanalization does not occur, the passageway does not form. This happens independently in each nasal cavity, so it can present as unilateral atresia, but often presents as **bilateral atretic choanae**

(aka bilateral choanal atresia). This is a disorder of embryology, and so generally presents as a **pediatric disease**. Because neonates are **obligate nose breathers** (they breathe through their nose unless they are crying), if there is an obstruction of airflow, the neonate will be unable to ventilate. This is classically taught as **blue with feeding**, **pink with crying**. When the neonate attempts to eat, the oropharynx is sealed to the nipple. If the choana is atretic, the baby becomes hypoxemic, presenting with cyanosis (blue baby). When the baby cries (often because of hypercapnia and not the hypoxemia), the baby pinks up. A scope can see the extent of the atretic segment, and often simply perforating a flimsy membrane is enough. In other cases, where the atresia is caused by the presence of bone, surgical resection may be required.

Nasopharynx

Just as we did with the nasal cavity, we want to first cover infections of the nasopharynx before moving into noninfectious causes. You've seen these infections before in Microbiology, but they are common enough conditions to be seen again, this time from the perspective of the epithelium rather than the perspective of the infecting agent. We then transition into nasopharyngeal carcinoma.

Pharyngitis and **tonsillitis** are common upper respiratory tract infections. They are most often caused by **viruses**—rhino and adeno. They are the same viruses that infected the nasal cavity, but have tropism for the squamous cell epithelium of the pharynx. The infected tissue gets **inflamed, boggy, and red**. It hurts to swallow (odynophagia), and the pain may radiate to the ears (a sign that the squamous epithelium of the eustachian tube may be implicated as well). Bacterial pharyngitis is one of the cornerstone considerations in outpatient medicine—do you culture, do you swab, do you give antibiotics, or do you let the virus pass? The Centor criteria are used to assess the likelihood that this infection is bacterial. If there are exudates on the tonsils, anterior chain lymphadenopathy, and no cough, chances are it's bacterial. Because the nasopharynx is lined with squamous epithelium, bacterial infections are commonly caused by group A *Strep. pyogenes* or *Staph. aureus*. Whether bacterial or viral, there will be **inflammation of the palatine tonsils** (the ones you can see in the back of your own mouth). If the tonsils become so enlarged that they obstruct breathing or exercise, they may be removed. **Tonsillectomy** is one of the most common pediatric ENT procedures.

Peritonsillar abscess. Sometimes, infections of the oropharynx get really bad. This is an abscess—a mass of mucosal tissue filled with pus—and needs to be drained. Because the nasopharynx is lined with squamous epithelium, infections are commonly caused by group A *Strep. pyogenes* or *Staph. aureus*. Abscesses tend to present with **higher fever** and **more toxicity** than their solely inflamed counterparts. It hurts to swallow and there is a mass effect, so **drooling** and a sore throat. The addition of the **hot-potato voice**, a sign of nasopharyngeal obstruction and **uvular deviation**, are clinical signs there is a mass effect. Imaging and surgical drainage are required.

Retropharyngeal abscess. The worst of the bacterial infections, it presents like a peritonsillar abscess—high fever, drooling, hot-potato voice—with a little extra. Instead of one tonsil's abscess pushing the uvula over, the patient will have their **neck flexed** to avoid pain and maintain their airway, and there will be **unilateral anterior chain lymphadenopathy**. Because the nasopharynx is lined with squamous epithelium, infections are commonly caused by group A *Strep. pyogenes* or *Staph. aureus*. This needs antibiotics and careful drainage of the abscess. There is drooling because it hurts to swallow. The neck is flexed to lift the abscess up and away from the anterior structures.

Otitis media. A middle-ear infection is more akin to a nasopharynx infection than an infection of the ear. Ascending the eustachian tube, the invader finds itself with the same epithelium it knows and loves, the stratified squamous found in the nasopharynx. Otitis media presents as **ear pain** that is **not worsened by pulling on the pinna**. The patient may complain of a feeling of fullness or difficulty

hearing. The best test is a physical exam, wherein the **tympanic membrane** is assessed with a puff of air. The connection between the middle ear and the outer ear, the tympanic membrane, is often **intact**, with the infection behind the tympanic membrane. This causes fluid, exudate, or pus to push up against the membrane. This presents as a tense membrane that does not budge with the puff of air. Treatment involves β-lactams to treat the usual offenders that infect respiratory epithelium—*Strep. pneumo*, *Moraxella*, and *Haemophilus*. In cases of severe infection or disability from the pressure, **ear tubes** can be placed. Intentional perforation of the tympanic membrane allows for drainage of the fluid out into the ear canal (because it obviously wasn't draining appropriately to the nasopharynx, where it should). This failure to drain is akin to the way rhinitis causes inflammation that blocks the sinuses. Here, inflammation in the eustachian tube prevents the drainage of fluid from the tube to the nasopharynx.

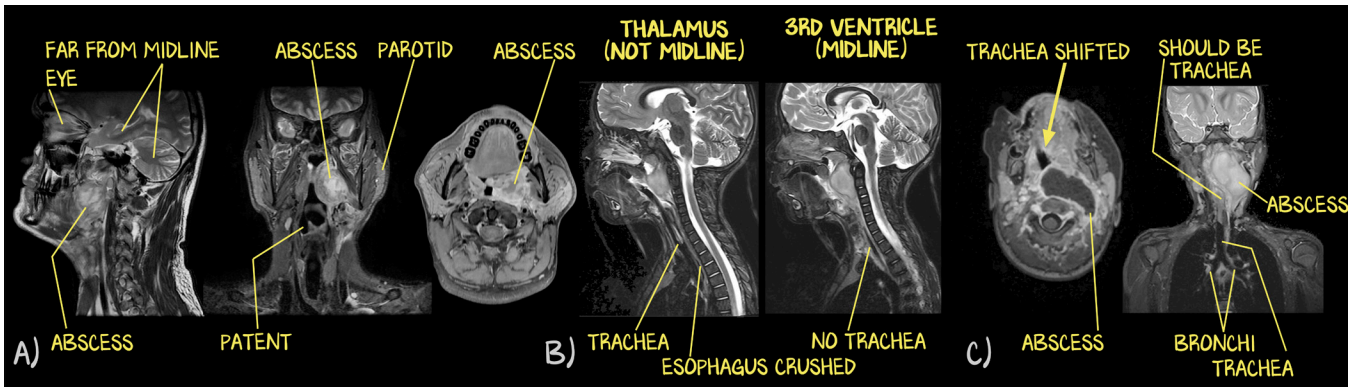

Figure 2.2: Abscesses of the Mouth
(a) T1-weighted MRI (CSF is black) of a patient with a peritonsillar abscess. It is critical to realize that a peritonsillar abscess is away from the midline. It may cause the uvula to shift, but it stays relatively clear of the airway. The remaining two figures are designed to prove the same point: unlike peritonsillar abscesses, retropharyngeal abscesses can deviate and even close the airway (b) T2-weighted MRI (CSF is white) in the sagittal plane. This midsagittal section (right) shows that when the brain is centered to midline (the third ventricle is visible), the trachea is not midline—it is not present in the film. When the thalamus is in view (left), the trachea is seen, indicating that it has been shifted. (c) In the T1-weighted axial MRI (left), the trachea has been shifted to the right (left side of image) by the abscess. In the T2-weighted coronal MRI (right), the larynx, trachea, and bronchi should all be seen in the same plane—the trachea and bronchi are, but the abscess is where the larynx should be.

Nasopharyngeal carcinoma is an **EBV-related** malignancy that is **not lymphoma**. And be really careful here, because it is a dangerous "gotcha" on licensure examinations. Ready? African child, growth on the face, EBV-related. What's that? *Obviously* Burkitt's lymphoma, right? Nope, just kidding, that's the exact same flashcard-learning for nasopharyngeal carcinoma, too. Nasopharyngeal carcinoma is also found in **southern China** in **adults who eat nitrosamines**. Asian, nitrosamine cancer? That was the Japanese gastric adenocarcinoma flashcard. Nasopharyngeal carcinoma is a wildcard disease. It is super-diddly-duper rare in the US. Learn this malignancy only as you attempt to get a 270 or better. Most students will not learn this cancer. Nitrosamines in Japan is stomach cancer. EBV face lesion in an African child is Burkitt's lymphoma. It's totally okay not to learn anything about nasopharyngeal carcinoma unless you plan on going into ENT or oncology, or plan on practicing in an endemic area. For those of you who insist on knowing more, it is a malignancy of the epithelium of the pharynx, so it will appear as nonkeratinized stratified squamous epithelium. It commonly spreads to the anterior lymph nodes, providing a convenient biopsy site. It grows across the choana, leading to difficulty with air movement through the nostrils. It can also erode up into the bones of the skull, causing paresthesia and pain in the face.

Larynx

You've probably got the theme by now: infections first, then growths.

Epiglottitis. The epiglottis has one purpose—to cover the larynx during swallowing to prevent the food bolus from going down the trachea. Its natural function, then, is to **obstruct the airway**. Now with the *Haemophilus* type B (HiB) vaccine, epiglottitis is a disease very rarely seen in the United States (vaccinate your children). However, from a mechanistic standpoint, it is extremely relevant for the ENT lessons. We covered this in detail in Microbiology: Bacteria #7: *GNR That Cause Serious Disease*. Now, in Pulmonary, we will focus on the anatomy. The normal epiglottis is pulled forward and up, away from the larynx, during respiration. It is pulled down and posterior to cover the larynx during swallowing. An uninflamed epiglottis has room to move back and forth. But there isn't a whole lot of space in the hypopharynx. So, if the epiglottis gets inflamed, it easily bumps into other structures (which hurts and can obstruct the airway). **It hurts to swallow** because it is inflamed, so the patient may be drooling. The swelling is on the anterior hypopharynx, so the patient will keep their head in **neck extension** in order to lift the epiglottis away from the other hypopharynx structures. The danger of this condition, more so than the retropharyngeal abscess, is that epiglottitis can **close the airway**. That means the patient **cannot breathe**. **Stridor** (inspiratory wheezing) signals impending airway closure. The caliber of the lower respiratory tract gets larger on inspiration as negative pressures pull it open. But above the larynx, negative pressures collapse the airway, and the larynx is narrower than the trachea below it. Stridor is an indication of **upper airway obstruction**, whether by the epiglottis or a foreign body. In epiglottitis, if you touch the epiglottis and inflame it any more than it already is, the patient will experience a total occlusion and stop breathing altogether. Skillful intubation is required, and the need for backup for surgical access to the airway prompts providers to **intubate patients in the OR**. That way, if the intubation is unsuccessful, they can perform a **tracheostomy** (a hole is made to put a tube through the cricothyroid cartilage). If performed in the ER, unsuccessful intubation would warrant a messier, less controlled, and very temporary **needle cricothyroidotomy** (think about breathing through a twizzler for more than 30 minutes) followed by the same surgical tracheostomy that should have been done in the first place. Epiglottitis, like retropharyngeal abscess, tends to happen in children **4–7 years old**.

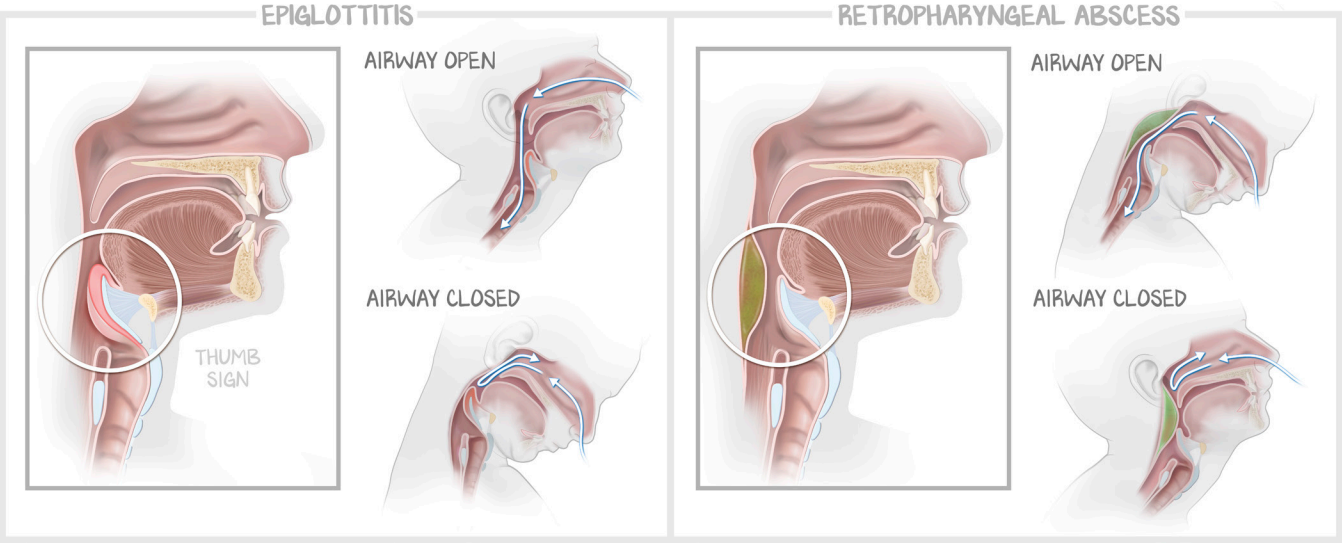

Figure 2.3: Epiglottitis and Retropharyngeal Abscess
The space the epiglottis occupies is already narrow, with many structures nearby. Inflammation of the epiglottis can obstruct airflow and cause secretions to remain in the mouth. Upon neck extension, the epiglottis is lifted from obstructing the airway. In retropharyngeal abscess, it is the reverse. The mass is in the posterior of the pharynx, so flexion opens the airway, extension obstructs.

Croup. Croup's formal name is **laryngo-tracheo-bronch-itis**. That would be inflammation (-itis) of the larynx, trachea, and bronchi (in the order in which air moves through them into the respiratory tract). So technically, this is both an upper and lower respiratory tract infection. The trachea has the largest-caliber lumen. Inflammation of the trachea would not cause obstruction. The bronchi are big—smaller than the trachea, but still have no risk of obstruction. The trachea has the largest-caliber lumen because the vocal cords narrow the lumen of the larynx above the trachea. They narrow the lumen! Oh no! Could they be the obstruction? The natural inclination is to think that laryngotracheobronchitis could be as deadly as epiglottitis. It isn't. The lumen of the larynx is still quite large. Inflammation of the vocal cords does limit the caliber of the lumen, but **not during quiet respiration** like in epiglottitis. Croup tends to infect slightly younger children, aged 6 months to 3 years. These kids have smaller airways than the kids that get epiglottitis, but the swelling caused by a virus is so much less than that caused by bacterial infection of the epiglottis. That means there will be **no inspiratory stridor**. But it is the already small airway that produces the classic symptoms. There is a loud sound when the child coughs. A cough is a forceful exhalation of a lot of air in a very short amount of time. The larynx is narrowed, just not enough to compromise the airway. When a lot of air moves all at once, across a narrowed lumen, it generates an abnormal sound. So, whenever the child coughs, it creates an "air murmur." This is described as a **seal-bark cough**. These kids are generally not as toxic, and simply walking outside on the way to the car to be evaluated may alleviate their symptoms. This is caused by **parainfluenza virus**.

Vocal cord nodules. There are three nodules we want you to know: overuse, papilloma, and cancer. **Overuse nodules** will always be **bilateral** and measure **less than 1 cm**. They are seen in patients who sing, yell, or otherwise start using their voice well beyond the average. The timing coincides with the insult, and the nodules will heal in a few days. They generally do not warrant enough investigation to scope, but because all of these vocal cord nodule conditions can cause **hoarseness**, it is easy to create a clinical vignette that warrants laryngoscopy, and the test writers can simply use the same vignette, but swap images of the scope or biopsy and ask you to tell the difference. **Papillomas** are caused by **HPV** (serotypes **6 and 11**) and are the wart equivalent of the vocal cords. The skin is squamous epithelium that keratinizes into corneocytes in a stratum corneum. The cervix, oropharynx, larynx, and anus are lined with a squamous epithelium that doesn't keratinize into corneocytes and doesn't have a stratum corneum. All have a stratum basale with the same type of stem cell. So, HPV can infect that cell and do what it does—induce excess replication of the stratum basale, forming a growth. Papillomas will be **unilateral** and measure **less than 1 cm**. Biopsy shows hyperplasia of the epithelium, but no malignant transformation. **Squamous cell carcinoma of the larynx** is caused either by **HPV** (serotypes 16 and 18 are the high-risk serotypes for malignancy in all nonkeratinized stratified squamous epithelium) or **cigarette smoking**. Squamous cell carcinoma is the obvious cancer for the vocal cords because they are already made up of squamous cells. But just as the bronchi may undergo squamous metaplasia from respiratory epithelium, so too can the vestibular folds, normally lined with respiratory epithelium, undergo squamous metaplasia. Thus, the cancer most often found "on the vocal cords" (either the true or false vocal cords) is going to be **squamous cell carcinoma**. The nodules are **unilateral** and **greater than 1 cm**. These, like their lung counterpart, will demonstrate desmosomes ("intercytoplasmic bridges") and keratin whorls if they get large enough. Additional risk factors for developing laryngeal carcinoma are **being male** and **alcohol** consumption.

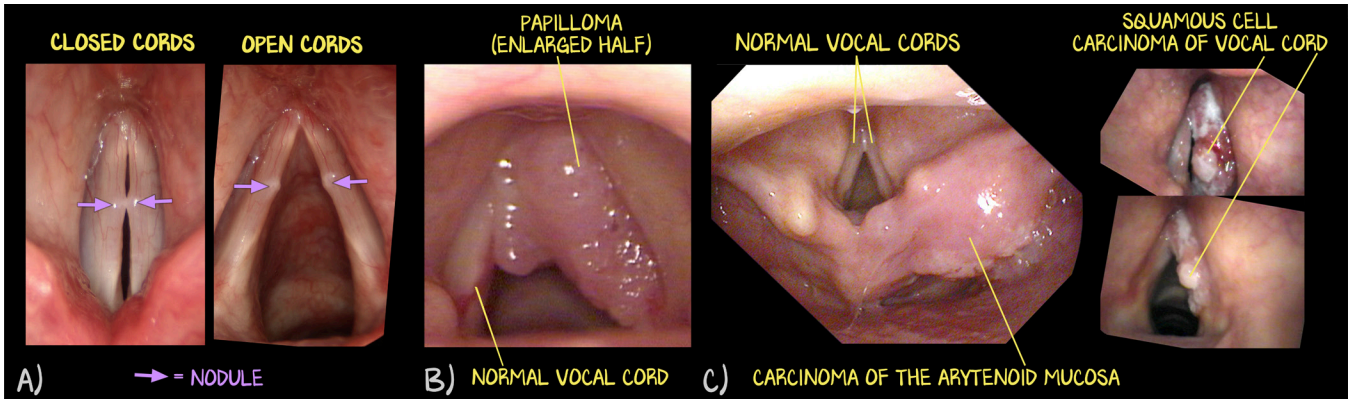

Figure 2.4: Laryngoscopy of Vocal Cords
(a) Open and closed vocal cords of a patient with an overuse injury. The nodules are small, symmetrical, and equal in appearance. (b) A unilateral lesion that is a little larger than usual, but nowhere near as large as most cancers. (c) Left, carcinoma of the mucosa of the aretynoids with no involvement of the vocal cords. Right, a unilateral and ugly lesion—a sign of cancer. This is small for a cancer (barely larger than the papilloma in panel b), but its non-uniformity (synonymous with ugly, in this case) gives it away. If allowed, it will continue to grow.

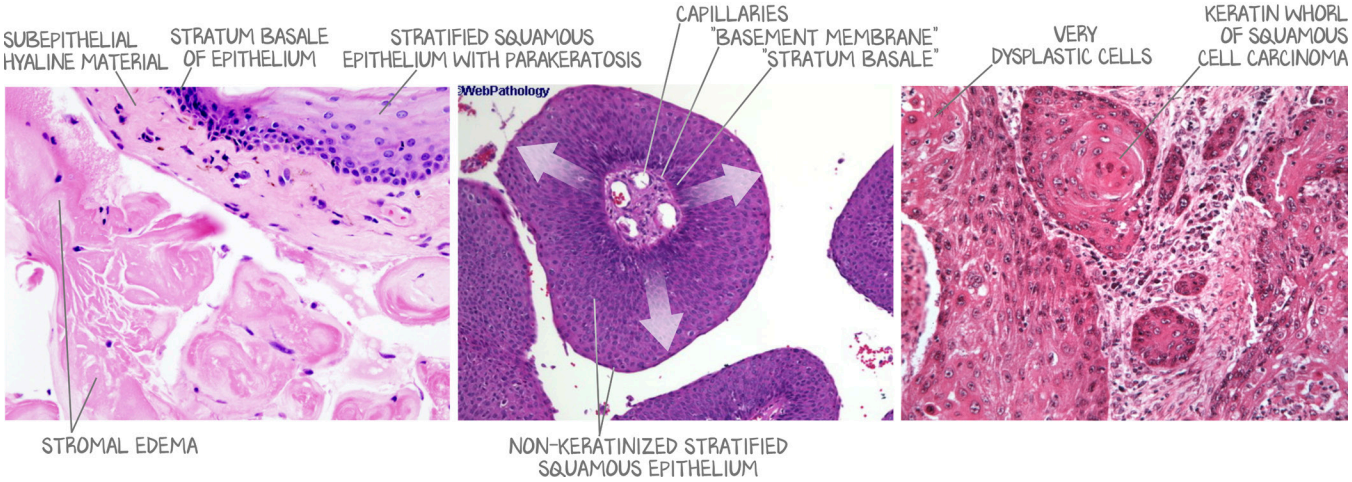

Figure 2.5: Histopathology of Vocal Cord Lesions
On the left is an H&E stain of an overuse nodule. Characteristic for these nodules, especially when they are chronic, is the subepithelial hyaline material—amorphous protein beneath the stratified squamous epithelium. Most of the histology shows stromal edema—white space (fluid) between mostly indiscernible connective tissue. The center panel is an H&E stain of a papilloma demonstrating proliferative and well-differentiated non-keratinizing stratified squamous epithelium overlying fibrovascular cores. The fibrovascular cores act as the blood supply to the epithelium. The basal cells anchor their basement membrane to the endothelial cells' and replicate to build their "epithelium." Proliferation is determined by the proximity and number of nuclei in the basale to the spinosum layer. On the right, typical of squamous cell carcinoma in any tissue, are the keratin whorls. Nothing tells us that the sample is from the larynx; all we know is that this is squamous cell carcinoma because of the whorls.

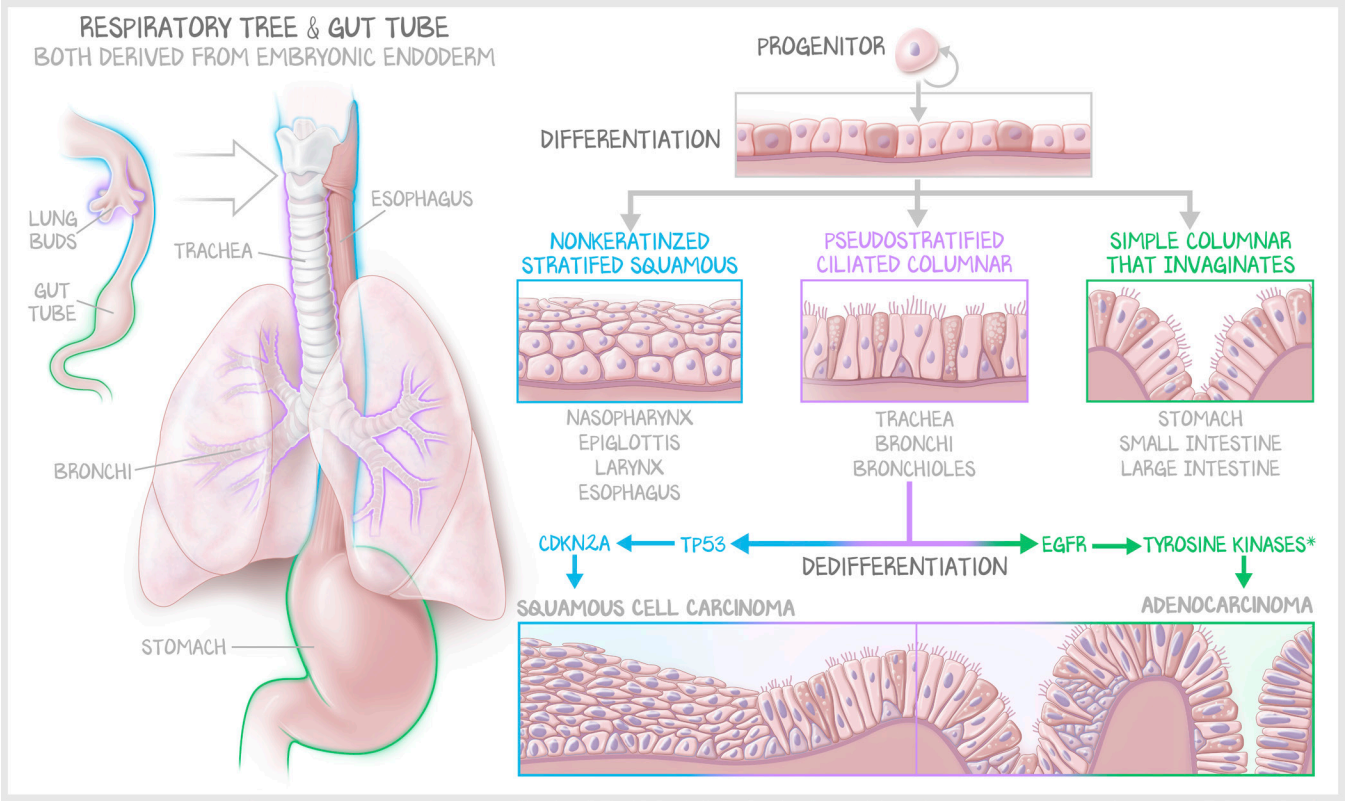

Figure 2.6: Embryology, Histology, and Epithelial Carcinoma of the Lung
Follow along with this illustration as you read the text below. We expect you to be approaching the end of your Basic Sciences curriculum, with Neuroscience and Reproduction remaining, and we wanted to take the opportunity to show you how well-connected things are.

The endoderm-derived gut tube will become the **GI tract**—from the oral cavity to the pectinate line—and the **respiratory tract** (aka appendages of the GI tract)—the nasal cavity, Eustachian tubes, and larynx, as well as all of the airway, including the trachea, bronchi, and bronchioles. There are three epithelial types, which are color-coded from the bud to the adult structures on the left side of the above illustration. As we look at the flow chart on the right, we see that a single pluripotent endoderm-derived precursor is capable of forming all of the GI and respiratory epithelia—oropharyngeal, respiratory, and glandular.

The pluripotent stem cell divided and differentiated a daughter cell that was genetically destined to become oropharyngeal mucosa (the **blue path**), which is **nonkeratinized stratified squamous epithelium**, the epithelium of the oral cavity, nasopharynx, oropharynx, pectinate line, and esophagus. That same pluripotent progenitor separately divided and differentiated a daughter cell that was genetically destined to become respiratory epithelium (**purple path**)—**pseudostratified columnar epithelium made up of ciliated columnar cells and goblet cells**. That original progenitor also separately divided and differentiated a daughter cell destined to become glandular epithelium (**green path**)—a **simple columnar epithelium that invaginates upon itself**, into its lamina propria, and is surrounded by the submucosa and muscularis externa—found in the stomach glands, the crypts (and evaginations of the villi) of the small intestine, and the crypts of the large intestine (crypt is a synonym for gland, dissimilar from an exocrine gland's acini or an endocrine-gland-rich capillary network). Genetic destiny is determined by the inactivation of segments of DNA (through various mechanisms, ignorance of which does not detract from the power of these paragraphs).

This matters because we can **justify and predict** what is most likely to occur in malignant transformation. If that respiratory epithelium is exposed to carcinogens, the accumulation of mutations that progress towards malignant transformation may be accelerated. By definition, a malignancy means there is **dedifferentiation**, enabling the epithelium to unlock genes previously sealed off by their differentiation during embryogenesis. And because gene activation and inactivation determine phenotypic expression (what the cells look like under a microscope), we can link gene mutation to phenotypic expression.

If that dedifferentiated precursor acquires mutations in *TP53,* then *CDKN2A*, then *RB*, the malignant respiratory epithelium will express the phenotype of **squamous cell carcinoma**. If that dedifferentiated precursor acquires mutations in *EGFR,* then other receptor-tyrosine-kinase-related genes (multiple genes encode either tyrosine kinase receptors or other proteins in their downstream pathways that are still in the same pathway, indicated by the asterisk in the illustration), then the malignant respiratory epithelium will express the phenotype of **adenocarcinoma**—adeno (gland-forming, invaginating simple columnar cells) carcinoma (cancer). Both epithelial carcinomas are derived from respiratory epithelium and express either squamous cell carcinoma or adenocarcinoma because that is the epithelium the original progenitor knew how to become. To become any other epithelium would mean severe dedifferentiation, which usually means anaplasia—the absence of a discernable phenotype. This also enables the use of known proteins expressed by each epithelium—using immunohistochemistry to stain tissue samples for suspected genetic anomalies (proteins expressed in the healthy tissue whose phenotype the cancer is expressing, proteins that are expressed by a cancer that aren't by healthy tissue), and develop molecular targets for treatment.

Remember in Lung #10: *Lung Cancer*, where we completely rearranged the lung cancer table according to epithelium vs. neuroendocrine vs. pleural cancers? This is why. The epithelium becomes an epithelial cancer because that's what those cells know how to become—the epithelia of the GI and respiratory tracts. Clinically, you will separate these cancers into smoking cancers and nonsmoking cancers, or by their responsivity to chemo and radiation, not on their embryonic or histologic origin. In the clinic, that is appropriate. But only after you master the mechanisms and the story of health and disease as told by the cells, the epithelium, and their genetic expression.

Medicine is not a firehose of knowledge. Rather, it is the repeated use of modular components—all unique in some ways and very similar in others. By telling the story of health and disease across the Organ Systems, one can gain an appreciation of the simplistic elegance of human life. Immensely complex, but also modular. Seemingly infinite permutations can be classified and remembered by their patterns and archetypes, with the most important variations bringing them within reach of human comprehension.